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Review

What does a comparison of the alcoholic Korsakoff syndrome and thalamic infarction tell us about thalamic amnesia?



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ABSTRACT

In this review, the clinical, neuropsychological, and neuroimaging findings in the alcoholic Korsakoff syndrome and in thalamic amnesia, resulting from focal infarction, are compared. In both disorders, there is controversy over what is the critical site for anterograde amnesia to occur—damage to the anterior thalamus/mammillo-thalamic tract has most commonly been cited, but damage to the medio-dorsal nuclei has also been advocated. Both syndromes show ‘core’ features of an anterograde amnesic syndrome; but retrograde amnesia is generally much more extensive (going back many years or decades) in the Korsakoff syndrome. Likewise, spontaneous confabulation occurs more commonly in the Korsakoff syndrome, although seen in only a minority of chronic cases. These differences are attributed to the greater prevalence of frontal atrophy and frontal damage in Korsakoff cases.

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1. Introduction

Twenty-five years ago, there was intense interest in the nature of diencephalic versus medial temporal amnesia (e.g. [Butters and](#)

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Brandt, 1985; Squire et al., 1989; Parkin et al., 1990a). But the emphasis has changed—for many years, we have had a journal called *Hippocampus*, but only briefly one called *Thalamus* (now defunct). There has seemed to be an assumption that the thalamus is simply a relay station in a memory network, controlled or orchestrated from within the hippocampi; but thalamic damage can cause a devastating amnesia, and this assumption may not be correct.

Within the neuropsychological literature, the alcoholic Korsakoff syndrome used to be regarded as the archetype of diencephalic amnesia, although there is now recognition that the pathology can be variable and may include concomitant damage to structures elsewhere, a problem which is true of all types of human amnesia (including those which result from herpes encephalitis, cerebral hypoxia, or focal stroke). The present paper will consider the alcoholic Korsakoff syndrome and thalamic infarction, comparing and contrasting the nature of the neuropsychological deficits, with the aim of better understanding the contribution of the ‘cognitive thalamus’ to memory processes. The paper will focus exclusively upon the study of human patients; other papers in this issue cover animal investigations and functional imaging studies in healthy participants.

2. The Korsakoff syndrome

2.1. Historical, clinical, and pathological findings

The alcoholic Korsakoff syndrome was described before Korsakoff by Lawson (1878) in the first volume of *Brain*. He described a syndrome resulting from alcohol misuse, which involved the “almost absolute loss of memory for recent events.” He showed perspicacity in arguing that: “In cases where organic change has been produced in the brain, the nature of the symptoms will be caused not so much by the character of the exciting cause as by the physiological functions of the regions diseased.” Moreover, Lawson anticipated the beneficial effects of thiamine by making the serendipitous observation that: “Marvellous results [can be] produced by a very highly concentrated essence of fresh meat.” However, possibly his patients felt better because, in addition, he advocated that this could be combined with “moderate doses of opium”!

Korsakoff (1887, 1889) himself described at least 30 alcohol-induced cases and 14 non-alcoholic cases of amnesic syndrome. In hindsight, the latter almost certainly had all suffered nutritional, i.e. thiamine, depletion. Korsakoff argued that: “At first, during conversation with such a patient . . . [the patient] gives the impression of a person in complete possession of his/her faculties; [the patient] reasons about everything perfectly well, draws correct deductions from given premises, makes witty remarks, plays chess or a game of cards, in a word comports himself [herself] as a mentally sound person.” However, “the patient constantly asks the same questions and repeats the same stories . . . may read the same page over and again sometimes for hours . . . is unable to remember those persons . . . met only during the course of the illness, for example, the attending physician or nurse.”

Korsakoff (1889) also elaborated on the nature of anterograde and retrograde amnesia, commenting: “The disorder of memory manifests itself in an extraordinarily peculiar amnesia, in which the memory of recent events, those which just happened, is chiefly disturbed . . . In other [cases], even the memory of remote events may also be disturbed . . . In very severe cases, the amnesia is much more profound; here, not only memory of recent events is lost, but also that of the long past . . . Thus, they may believe themselves to be in the setting (or circumstances) in which they were some 30 years ago, and mistake persons . . . around them now for people . . .

at that time.” This also relates to Korsakoff’s views on confabulation (see below).

Korsakoff (1889) mentioned in passing “prodromal agitation and confusion,” ophthalmoplegia, nystagmus, and ataxia; but he did not attribute the description of these features to Wernicke (1881), who had reported them some years earlier in two alcoholic patients and one patient with pyloric stenosis. Subsequent studies gave widely varying prevalence rates for these features preceding the Korsakoff syndrome (Riggs and Boles, 1944; Cravito et al., 1961; Victor et al., 1971; Cutting, 1978). In recent years, Caine et al. (1997) have attempted to operationalise diagnostic criteria for Wernicke’s syndrome.

Moll (1915) described 30 cases of alcoholic Korsakoff syndrome, arising in South Africa. Most had had a delirious onset (consistent with a Wernicke confusional state). In a minority of cases, the mental symptoms “developed in a gradual manner, without (the) acute initial stage.” Anterograde memory was particularly affected, but the retrograde amnesia covered several years—in some cases, most of the patient’s adult life. Moll commented that the confabulations in such cases were “very striking”. These consisted of the distorted recollections of real facts, or true recollections, wrongly oriented in time or place. They were “usually within the bounds of the conceivable”, often with strong emotional content (see Sub-section 2.4.2). As many others have noted, the confabulations subside with time. Moll also noted that many Korsakoff patients showed improvement with time, if they refrained from alcohol.

In the 1930s and early 1940s, animal experiments suggested the critical role of thiamine depletion in producing the Korsakoff syndrome (Alexander et al., 1938; Alexander, 1940). However, the findings were not unequivocal, and it was wartime studies that really demonstrated the importance of thiamine replacement in the management of the condition (De Wardener and Lennox, 1947; Cruikshank, 1950). De Wardener and Lennox (1947) reported 52 cases of the Wernicke or Korsakoff syndrome in Changi Prison, Singapore, and they had their records in a Thai cemetery until after the war. The onset of Wernicke signs (confusion, ataxia, nystagmus, and ophthalmoplegia) occurred after a mean of approximately 6 weeks, and a severe memory disorder (Korsakoff syndrome) after a further 2–3 weeks. Confabulation was seen in approximately 25% of cases. Outcome was closely related to the availability of thiamine (supplied by the Red Cross). When patients were untreated, 80% died. When at least some treatment in the form of oral tablets or Marmite was available, 60% of cases died, and 40% were said to be ‘cured’. When injectable thiamine was available, 30% died, and 68% were cured, with 1 case (2%) surviving but uncured.

Whilst Victor et al. (1971) clearly distinguished between Wernicke’s encephalopathy and the alcoholic Korsakoff syndrome, they pointed to the overlap in the underlying neuropathology of these two syndromes. They defined the Korsakoff syndrome as “an abnormal mental state in which memory and learning are affected out of all proportion to other cognitive functions in an otherwise alert and responsive patient.” They pointed to the importance of the thalamus in the underlying aetiology of the anterograde amnesic syndrome, stating that all 24 patients with lesions in the medio-dorsal thalamic nucleus at autopsy had exhibited a persisting memory disorder (Korsakoff syndrome) in life. On the other hand, five patients with mammillary body lesions, in whom the medio-dorsal thalamic nuclei were spared, experienced a transient Wernicke’s syndrome, without going on to manifest a permanent amnesia. However, subsequent investigators have criticised the Victor et al. (1971) study for lacking detailed neuropsychological findings to place alongside their neuropathological observations.

Furthermore, more recent investigations have shown that the Korsakoff syndrome is not always preceded by Wernicke’s encephalopathy. Both Wallis et al. (1978) and Torvik et al. (1982) pointed out that many patients are initially admitted to

hospital under the care of physicians in a confusional state or coma. They may have had a concurrent chest infection, fever, or head injury. Only as their confusion resolves does the underlying Korsakoff syndrome become evident. Moreover, Cutting (1978) argued that some cases have a “gradual” or insidious onset (compare Moll, 1915). There may have been a transient episode of Wernicke features in the community, and these (more insidious) cases are more likely to come to the attention of psychiatrists or clinical psychologists. Finally, both Harper et al. (1987) and Torvik et al. (1982) showed that, whilst only 1–2% of alcoholics obtain a diagnosis of the Korsakoff syndrome during life, 12–15% of autopsies in heavy drinkers reveal the characteristic neuropathological features of the Wernicke–Korsakoff syndrome. Presumably, these patients suffered memory complaints during life, but were never diagnosed. The alternative interpretation would be that the underlying neuropathology does not always produce the classical clinical manifestations; but, interestingly, Pitel et al. (2011) have shown that the presence of Wernicke signs in non-Korsakoff alcoholics is associated with memory and other cognitive impairments.

The characteristic neuropathological pattern of findings in the Wernicke and Korsakoff syndromes consists of neuronal loss, gliosis, and micro-haemorrhages in the paraventricular and peri-aqueductal grey matter (Victor et al., 1971). There is often concomitant cortical atrophy, especially frontally; and there may be loss of large neurons in the superior frontal cortex, hypothalamus and cerebellum, loss of prefrontal white matter, and neuronal dendritic shrinkage (Victor et al., 1989; Torvik et al., 1982; Harper et al., 1987, 1988; Harper and Corbett, 1990; Harper, 2009). The finding of concomitant frontal changes is consistent with the neuropsychological finding of associated executive impairments (Kopelman, 1991; Van Oort and Kessels, 2009; Oscar-Berman, 2012).

As already mentioned, Victor et al. (1971) indicated that the medio-dorsal nucleus of the thalamus might be the critical site of pathology causing the anterograde amnesia in Korsakoff's syndrome. However, Mair et al. (1979), and later Mayes et al. (1988), employed the combination of detailed (ante-mortem) neuropsychological assessment with detailed autopsy investigations in two Korsakoff patients in each study (four patients across the two studies). In contrast to Victor et al. (1971), these authors identified lesions within the mammillary bodies, the mammillo-thalamic tract, and the anterior thalamus as critical to the anterograde amnesia. Consistent with this, Harding et al. (2000) compared five ‘Wernicke only’ patients with eight Korsakoff patients who had persisting memory disorder, finding that the critical difference between the two groups was in the anterior (principal) thalamic nuclei, i.e. these nuclei were always damaged in the Korsakoff cases, but never in the ‘Wernicke only’ patients. This indicated that these nuclei might be the critical site of damage giving rise to the anterograde amnesia. The authors noted that the anterior (principal) nucleus lies at the head of the circuitry connecting the mammillary bodies, the mammillo-thalamic tract, and the thalamus. The conflict between Victor et al.'s (1971) findings and those of the more recent studies may be attributable to different techniques of investigation, but it is also echoed in the literature on thalamic infarction (see below).

2.2. Korsakoff syndrome—neuroimaging

Early quantified CT brain investigations indicated a variable degree of cortical atrophy (ventricular enlargement and sulcal widening) in Korsakoff patients, with the frontal lobes often being particularly severely affected (Jacobson and Lishman, 1987; Jacobson et al., 1990; Shimamura et al., 1988). Women drinkers were likely to be affected at a younger age by this cortical atrophy (Acker, 1985). Early MRI investigations also showed a variable degree of cortical atrophy, with a ‘block’ of tissue which

encompassed diencephalic structures (including the thalami) being particularly affected (Jernigan et al., 1991). Colchester et al. (2001), in a detailed quantitative MRI investigation, showed atrophy in the thalami and mammillary bodies, and left and right frontal lobe atrophy, with temporal lobe structures (anterolateral temporal lobe volume, parahippocampal and hippocampal volumes) not differing significantly from control values. In subsequent papers, brain volumes in these structures were related to scores on tests of anterograde and retrograde memory, respectively (Kopelman et al., 2001, 2003).

In the Wernicke phase of the disorder, Sullivan and Pfefferbaum (2009) and Jung et al. (2012) have identified signal alteration in key regions within the limbic circuitry. Hyper-intense signal was found in the mammillary bodies, the thalami, the periventricular grey matter, the fornix, and the colliculi. (Such signal alteration is not generally seen in the chronic Korsakoff phase.) In the more chronic (Korsakoff) phase, Sullivan and Pfefferbaum (2009) and Jung et al. (2012) have reported mammillary body atrophy, ventricular enlargement, and sulcal widening in Korsakoff patients. On quantified analysis of regional atrophy in Korsakoff patients, non-Korsakoff alcoholics, and healthy controls, Sullivan and Marsh (2003) and Sullivan and Pfefferbaum (2009) demonstrated significant atrophy in Korsakoff patients (relative to the other two groups) in the mammillary bodies, the thalami, and also in the hippocampi. Non-Korsakoff alcoholics showed a lesser degree of atrophy in these brain regions, relative to healthy controls (although there was no difference between Korsakoff and non-Korsakoff alcoholics in mammillary body volume in an earlier study using cruder ratings; Shear et al., 1996). Colchester et al. (2001) also found thalamic and mammillary body atrophy in Korsakoff patients, but did not find statistically significant hippocampal atrophy, which may simply demonstrate variability across individual patients. Colchester et al. (2001) also showed statistically significant correlations between regional brain volumes and a range of anterograde memory tasks, including a correlation of 0.58 ($P=0.025$) between thalamic volume and the delayed memory index on the Wechsler scale.

In a more recent investigation, Pitel et al. (2012) found widespread grey and white matter volume loss in both Korsakoff and non-Korsakoff alcoholics, compared with healthy controls. The Korsakoff group showed disproportionate grey matter volume loss only in the medial portion of the thalami, the hypothalamus (including the mammillary bodies) and left insula. There were disproportionate white matter changes only in the corpus callosum and left thalamic radiation. Furthermore, in an interesting cross-national comparison, Le Berre et al. (2014) found that French and U.S. Korsakoff patients had similarly reduced thalamic volumes (and smaller thalamic volumes in the French non-Korsakoff alcoholics than in their U.S. counterparts). However, the U.S. Korsakoff patients showed more widespread changes with smaller hippocampal, amygdala, and cerebellar vermis volumes. The authors postulated genetic, ethnic, nutritional, or treatment adequacy as possible factors giving rise to these differences. There might also be diagnostic differences: although all the patients were diagnosed according to DSM (Diagnostic and Statistical Manual) criteria, details of background neuropsychological test performance were not given.

Reed et al. (2003) examined 18-fluoro-deoxy-glucose metabolism on positron emission tomography (PET), finding reduced glucose uptake in a region encompassing the thalami bilaterally, the hypothalami, and the mammillary bodies, the basal forebrain, and the retrosplenium, the latter being another ‘relay station’ within limbic circuitry (Valenstein et al., 1987). More recently, Pitel et al. (2009) examined nine patients using FDG-PET, in whom they also had grey and white matter MRI measurements. They also found hypometabolism in the thalami, mammillary bodies and orbitofrontal cortex. But they also showed hypometabolism

in the superior middle frontal cortex, supplementary motor area cingulate, precuneus, left middle and inferior temporal lobe, calcarine cortex, lingual gyrus, and middle occipital cortex. In general, these changes paralleled grey matter density changes on MRI. The only PET hypometabolism changes found consistently in all nine patients were in the superior frontal gyrus, middle cingulate gyrus, and the precuneus. Moreover, the metabolic change in the middle cingulate gyrus was disproportionately severe relative to MRI change in that region.

In summary, MRI studies have revealed signal alteration in critical brain structures (the thalami, mammillary bodies, periventricular grey matter, and fornix) in the acute Wernicke phase of the disorder (Sullivan and Pfefferbaum, 2009). In the more chronic (Korsakoff) phase, various studies have identified brain atrophy in the thalami, mammillary bodies, and frontal cortex (Jernigan et al., 1991; Colchester et al., 2001; Sullivan and Marsh, 2003; Pitel et al., 2012). There are also widespread grey and white matter changes, which are seen in both Korsakoff and non-Korsakoff alcoholics, more severely in the former group (Jacobson and Lishman, 1987; Pitel et al., 2009, 2012). U.S. studies appear to implicate hippocampal atrophy (Sullivan and Marsh, 2003) more commonly than in U.K. (Colchester et al., 2001) or French investigations (Le Berre et al., 2014). Similarly, a common theme in FDG-PET investigations is reduced glucose uptake in the thalami bilaterally, the hypothalamus, the mammillary bodies, and the basal forebrain/orbito-frontal cortex (Reed et al., 2003; Pitel et al., 2009); but more widespread changes have been reported by Pitel et al. (2009), many of which are associated with parallel grey matter density changes on MRI.

2.3. Korsakoff syndrome—neuropsychological aspects

2.3.1. Anterograde amnesia

Over the years, there has been considerable interest in the pattern of neuropsychological deficit in Korsakoff patients (Huppert and Piercy, 1976, 1978a,b; Butters and Cermak, 1980; Parkin et al., 1990a,b). In general, both recall memory and recognition memory are impaired (Kopelman, 1989), which may reflect the involvement of differential circuitry, implicating recollective and familiarity processes (Aggleton and Saunders, 1997). An important point is that non-Korsakoff alcoholics also exhibit thalamic and cortical changes and they show a range of neuropsychological impairments. However, Korsakoff patients exhibit disproportionate deficits at episodic memory tasks (Butters and Cermak, 1980; Pitel et al., 2008; Fama et al., 2012), consistent with Victor et al.'s (1971) definition.

A characteristic finding has been that performance on span tasks is preserved (Baddeley and Warrington, 1970; Kopelman, 1985), reflecting the relative preservation of 'primary' or 'short-term' memory. However, Pitel et al. (2008) and Brion et al. (2014) have reported that there are 'working memory' impairments, but no more severe than those seen in non-Korsakoff alcoholics. An early debate concerned whether 'short-term' forgetting was affected or not, some authors arguing for preservation (Baddeley and Warrington, 1970), and others demonstrating impaired performance across a number of different tasks (Butters and Cermak, 1980). Subsequent studies suggested that there was relative preservation in these terms, but that performance by Korsakoff groups tended to be affected after about 20 s delay on both verbal and non-verbal material (Kopelman, 1985, 1989). It was argued that impaired performance on 'short-term' tasks reflected a degree of concomitant cortical atrophy, rather than being the consequence of the primary pathology within mammillary body/thalamic circuits (Warrington, 1982; Kopelman, 1985).

In terms of longer-term forgetting, Huppert and Piercy (1978a) demonstrated that, after initial learning had been 'matched' to controls by giving Korsakoff patients prolonged exposure times to pictorial material, their rate of forgetting was 'normal'. This

was essentially replicated by others (Kopelman, 1985; McKee and Squire, 1992). Subsequent studies showed that forgetting was normal on recognition memory tasks using verbal, pictorial, or abstract material (after 'matching' of initial learning by prolonged exposure times to Korsakoff patients) over a period of approximately 20 min. However, on recall memory tasks, Korsakoff patients (and also those with medial temporal pathology) showed accelerated forgetting at intervals between approximately 20/25 s and 10–20 min (Kopelman and Stanhope, 1997; Green and Kopelman, 2002). In brief, this means that the Korsakoff patients have a severe deficit in learning new material and, on top of this, they also have difficulty in retaining and retrieving it, when tested on recall memory tasks, at intervals beyond about 20–25 s.

2.3.2. Context memory

Korsakoff (1889) commented that, in some instances, patients could remember events, "but not the time when they occurred." Memory for context can affect both anterograde and retrograde memory, and a deficit in temporal context memory may underlie the occurrence of spontaneous confabulation (see below).

There has also been considerable interest in context memory in Korsakoff patients. Huppert and Piercy (1976, 1978b) found a high rate of false positives on recognition memory testing of familiar material in this patient group. Moreover, when they showed pictures three times on Day 1, and asked subjects to make recency judgements for material presented on Day 2, they found a significantly raised rate of false positives in the Korsakoff patients, mistaking frequently presented for recently presented material. This finding was essentially replicated by Meudell et al. (1985), who also showed that controls with a 'weak' memory (i.e. tested at a week's delay) did not show the same specific deficit in recency judgements (or temporal context memory). Similarly, Shoaieir and Mayes (1991) found that Korsakoff patients showed impaired recall and disproportionate errors on a spatial context memory task.

Parkin et al. (1990a) argued that Korsakoff patients were disproportionately impaired in memory for temporal sequence, whereas patients with temporal lobe pathology were disproportionately impaired on spatial memory tasks. Kopelman et al. (1997) examined this further. These authors presented line drawings at the top and bottom portion of a slide in two series (T1, T2), 45 min apart. In order to 'match' the 'target recognition' memory performance of patient groups to healthy controls, the exposure times to these slides (at T1 and T2) was 'titrated', such that the patient groups received longer initial presentations of the material. T2 was presented approximately 45 min after T1, and then, after a further 10 min delay, recognition memory testing and context identification (Which list did a particular slide come from? Was it at the line drawing at the top or bottom of the slide?) were carried out. The 'target' recognition memory testing performance of the patient groups (including Korsakoff patients) did not differ significantly from healthy controls, but the Korsakoff patients were significantly impaired at identifying which temporal series a slide had been in (a temporal context memory deficit). In terms of identifying the position on the slide, the Korsakoffs' performance was approximately mid-way between that of healthy controls and patients with temporal lobe pathology (who were significantly impaired at this task), although the Korsakoff difference from the controls was not statistically significant on the spatial task.

Somewhat similarly, Chalfonte et al. (1996) showed that, in making judgements on a spatial array, Korsakoff patients showed a trend towards impairment, but did not differ significantly from alcoholic controls. On the other hand, patients with medial temporal lesions did differ significantly from controls on 'incidental' judgements of spatial position. By contrast, Kessels et al. (2000) showed impairment in memory for object locations in Korsakoff patients, compared with healthy controls, on a task very similar to

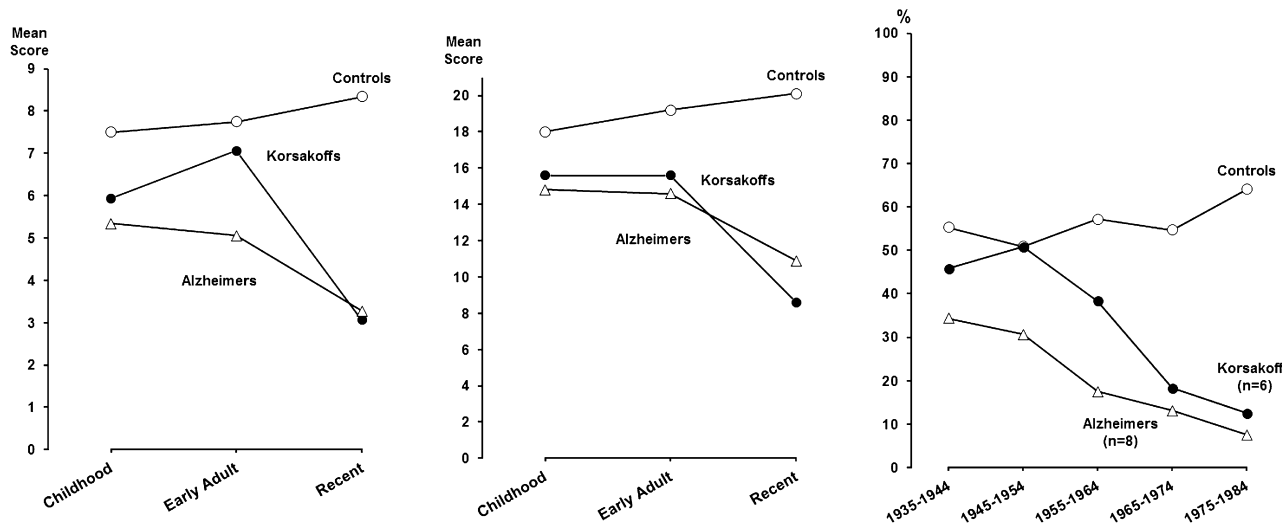


Fig. 1. Retrograde amnesia: temporal ('Ribot') gradients across different remote memory tasks. Autobiographical incident recall; personal semantic fact recall; news event recall (Kopelman, 1989).

that of Chalfonte et al. Likewise, Pitel et al. (2008) showed impairments in Korsakoff patients, relative to both healthy controls and non-Korsakoff alcoholics, on both temporal and spatial recognition memory tasks.

In summary, temporal context memory has been affected in virtually all studies of Korsakoff patients, whereas there are more variable findings in studies investigating spatial context memory.

2.3.3. Retrograde amnesia

Ribot (1882) put forward a 'law', which stated: "The progressive destruction of memory follows a logical order—a law ... It begins with the most recent recollections which, being ... rarely repeated and ... having no permanent associations, represent organisation in its feeblest form."

Although the earliest quantified investigation of retrograde amnesia, studying a 'mixed' group of amnesic patients, showed a 'flat' temporal gradient (Sanders and Warrington, 1971), subsequent investigations have generally found a 'steep' temporal (or Ribot) gradient in Korsakoff patients with relative sparing of early memories (Albert et al., 1979; Butters and Cermak, 1980, 1986). Butters and Cermak (1986) studied a Korsakoff patient who had written his own autobiography some years earlier. Consequently, it was possible not only to check his memory for remote autobiographical events against his earlier recollection, but also to demonstrate that his post-Wernicke temporal gradient could not have simply been the consequence of a progressively severe problem in storing memories as his drinking had become heavier. This finding is consistent with the observation that there is not any significant correlation between retrograde memory performance and the estimated duration of heavy drinking (Kopelman, 1989). Moreover, a retrieval deficit in remote memory is suggested by improved performance in response to recognition or contextual cues (Kopelman, 1989; Parkin et al., 1990b; Race and Verfaellie, 2012).

This temporal or 'Ribot' gradient can be demonstrated across different components of remote memory. Fig. 1 shows patterns of performance by Korsakoff patients, Alzheimer patients, and healthy control participants in the recall of autobiographical incidents, personal semantic 'facts', and news event episodes of short duration (Kopelman, 1989). In this investigation, the Alzheimer patients showed a statistically significant interaction, whereby they performed relatively worse than controls at 'recent', compared with

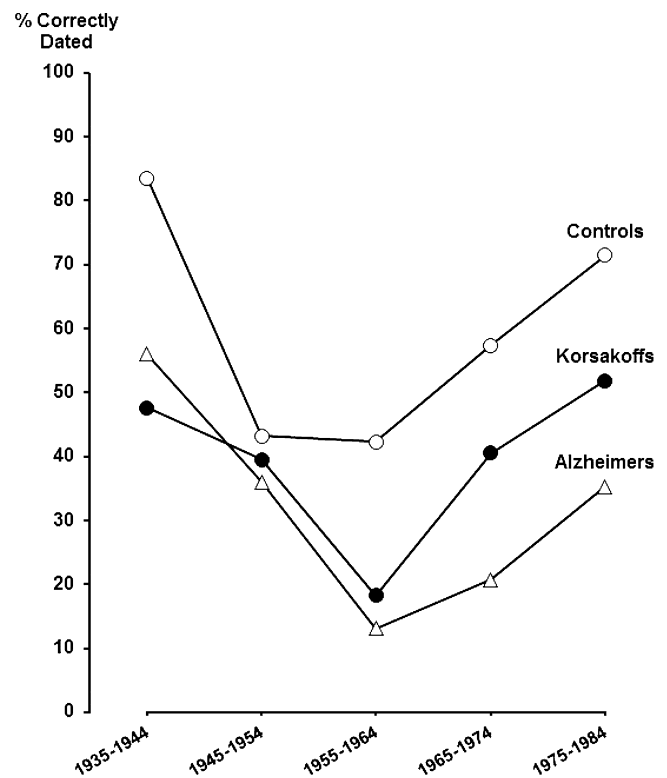


Fig. 2. Retrograde amnesia: Dating of news events identified correctly on a recognition memory task (Kopelman, 1989).

remote (childhood/early adult) events and facts. The Korsakoff patients showed a 'steeper' temporal gradient across all three tasks, and the news event test indicated that their impairment went back 20–25 years before the onset of the Wernicke phase of their disorder.

In the latter study, Korsakoff patients' ability to date news events that they had correctly identified (within a 5-year range) was also investigated. Fig. 2 shows that, like the control and Alzheimer participants, they showed a U-shaped curve, performing better at dating earlier and more recent than intermediate events (a primacy and recency effect) but, nevertheless, they performed significantly worse overall than the healthy participants at this task. In other

words, there was a temporal gradient for the correct recognition of news events, but a U-shaped curve for dating items which had been correctly recognised (i.e. excluding items not recognised/identified). [Parkin et al. \(1990b\)](#) was also interested in the contextual aspect of remote memory, asking whether a contextual memory deficit contributed to Korsakoff patients' retrograde amnesia. Parkin and colleagues showed famous faces to Korsakoff patients and healthy controls, either in context (e.g. Elvis Presley shown strumming a guitar) or out-of-context (e.g. Elvis Presley's face shown without any external context). [Parkin et al. \(1990b\)](#) showed that Korsakoff patients benefited from the provision of contextual cues, particularly for more remote memories, as did healthy controls, but that a contextual memory deficit could not explain the severity and pattern of this retrograde amnesia.

It is possible to examine the extent to which volume loss in specific brain regions is associated with impaired performance on remote memory (retrograde amnesia) tasks. [Kopelman et al. \(2003\)](#) showed that a multiple regression based on frontal, thalamic, and medial temporal volumes on MRI predicted 60.1% of autobiographical incident variance, 59.2% of personal semantic fact variance, and 47.9% of news event recall variance in Korsakoff patients—frontal volumes, and then thalamic volumes, making the greatest contribution to total variance. Interestingly, these findings were consistent with those in an earlier study ([Kopelman, 1991](#)), which showed that performance on executive tests could predict 68.5% of the variance in Korsakoff patients on autobiographical and remote memory tasks, compared with only 21% of variance predicted by performance on anterograde memory tests. [Fama et al. \(2004\)](#) carried out a related study, examining the performance of five Korsakoff patients on a test of Famous Presidents. They also found that remote memory impairment was not correlated with the severity of anterograde memory impairment. Naming the Presidents showed a significant rank correlation with posterior cortical white matter volume, and sequencing them with prefrontal white matter volume, and anterograde memory with hippocampal volume; but these correlations were based on only five patients.

Taken together, these findings suggest a hypothesis whereby damage to mammillary body/anterior thalamic pathways produces a deficit in new learning or the 'binding' of associations i.e. anterograde amnesia; whereas damage to thalamic-frontal or thalamic-cortical projections, or severe frontal lobe atrophy, produces a superimposed retrieval deficit, resulting in an extensive (temporally graded) retrograde amnesia. (See also [Race and Verfaellie, 2012](#), for a valuable further discussion of the retrograde amnesia in the Korsakoff syndrome.)

2.4. Confabulation

2.4.1. Definitions and pathology

Confabulation is often thought of as pathognomic of the Korsakoff syndrome, although this is not correct. Confabulation refers to false or erroneous memories arising involuntarily (i.e. not deliberately) in the context of a neurological amnesia. The memories may be false in themselves or 'real' memories jumbled and confused in temporal context and retrieved inappropriately. Spontaneous confabulation refers to a persistent, unprovoked outpouring of erroneous memories which "may reflect an extremely incoherent and context-free retrieval of memory and association" ([Kopelman, 1987](#)). Momentary or 'provoked' confabulation refers to fleeting intrusion errors or distortions, which occur in response to a challenge to memory, such as in a memory test.

Over recent decades, clinical, neuropsychological, and neuroimaging investigations have indicated that damage within the frontal cortex, rather than within mammillary body/thalamic pathways or the 'extended' hippocampi, results in spontaneous confabulation. [Luria \(1976\)](#) described how large pituitary tumours,

especially those extending anteriorly, and medial frontal lesions gave rise to a florid confabulatory syndrome—"a gross disturbance of ... active recall." [Stuss et al. \(1978\)](#) described five patients with spontaneous or 'fantastic' confabulation. Neuropsychological testing, CT brain scan and/or EEG, all showed evidence of executive dysfunction/frontal pathology; in particular, all showed severe impairment on the Wisconsin Card Sorting Test. These authors reported that, as one patient improved in his memory test scores, there was not any corresponding change in his confabulation. By contrast, [Kapur and Coughlan \(1980\)](#) described a single case study, in whom confabulation declined as executive test scores (card sorting, cognitive estimates) improved. [Baddeley and Wilson \(1986\)](#) described two patients in whom spontaneous confabulation was associated with large frontal lesions; one of these patients denied that he was married to his wife. More recent reviews of neuroimaging findings have indicated a critical role of the ventro-medial and/or orbito-frontal regions in giving rise to confabulation ([Gilboa and Moscovitch, 2002](#); [Schneider, 2003](#); [Turner et al., 2008](#)). For example, [Turner et al. \(2008\)](#) investigated a series of 38 patients with frontal lesions, 16 with posterior lesions, and 50 healthy controls, finding that confabulations were much more frequent in the 'frontal' than 'posterior' group, and much more common in orbital or medial lesions within the frontal lobes than in those with more lateral frontal pathology.

More particularly, [Gilboa et al. \(2006\)](#) compared the sites of pathology in four patients who confabulated as a result of anterior communicating artery aneurysms with seven patients who had similar aneurysms but no confabulation. They found that a small region in the ventro-medial frontal cortex was always affected in the confabulating group, but never in the non-confabulating patients. Similarly, [Toosy et al. \(2008\)](#) showed hypometabolism (reduced glucose uptake) in a similar ventro-medial frontal region in a patient with florid confabulation.

2.4.2. Theories of confabulation

Theories of confabulation fall within four broad groups: (i) those that emphasise context memory confusions ([Schneider et al., 1996, 2000](#)) or a malfunction in 'temporal consciousness' ([Dalla Barba et al., 1997](#); [La Corte et al., 2011](#)); (ii) those that emphasise a problem in trace specification or verification—the editing out of errors (e.g. [Burgess and Shallice, 1996](#); [Schacter et al., 1998](#); [Moscovitch and Melo, 1997](#); [Gilboa et al., 2006](#)); (iii) those which emphasise motivational factors ([Conway and Tacchi, 1996](#); [Fotopoulou et al., 2004, 2007](#)); and (iv) interactionist accounts, emphasising a combination of factors (e.g. [Johnson et al., 1997](#); [Kopelman et al., 1997](#)).

[Korsakoff \(1889\)](#) put forward what would now be seen as a 'context confusion' account of confabulation. He emphasised the confusion of "old recollections with present impressions." He described a patient who "in telling of something about the past, ... would suddenly confuse events and would introduce the events related to one period into the story about another period ... Telling of a voyage she had made to Finland before her illness and describing her voyage in fair detail, the patient mixed into the story her recollections of Crimea, and so it turned out that in Finland people always eat lamb and the inhabitants are Tartars."

A similar temporal context confusion account of confabulation has also been made by a number of other clinical writers (e.g. [Moll, 1915](#); [Talland, 1965](#); [Victor et al., 1971](#)). [Schneider et al. \(1996\)](#) provided a 'test' based on this theory: they carried out two 'runs' of a continuous recognition memory task, in which, during the second 'run', previous distractors became targets and targets became distractors in order to provoke false positive responses. The authors showed that five confabulating patients were clearly differentiated on this task from other (non-confabulating) amnesic patients and healthy controls in terms of the relative number of false positive responses in the second 'run' of this recognition memory test

(see also Bouzerda-Wahlen et al., 2013). However, Gilboa et al. (2006) showed that non-confabulating patients with anterior communicating artery aneurysms overlapped with both confabulating patients and healthy controls in performance on this task.

Trace specification/verification theories have emphasised problems in trace specification (or cue-retrieval), strategic search, and the monitoring of errors (Burgess and Shallice, 1996; Moscovitch and Melo, 1997). In particular, Gilboa et al. (2006) placed emphasis upon a deficit in pre-conscious, post-retrieval monitoring of responses, giving rise to confabulation; and these authors also found a high rate of false positives on a Schnider-type test where discriminations had to be made on the basis of (difficult to differentiate) visual perceptions (rather than temporal order).

Motivational accounts of confabulation have emphasised a combination of editing and motivational factors. For example, Conway and Tacchi (1996) argued that their patients' confabulations transformed "the present into a time of harmony and comfort rather than discord and distress." In a series of investigations, Fotopoulou et al. (2004, 2007, 2008) have argued that confabulations are more likely to include pleasant experiences and/or positive self-representations, and the inappropriate retrieval of pleasant autobiographical memories. For example, Fotopoulou et al. (2008) administered positive, negative, and neutral stories about others or the self to 15 confabulating patients, four non-confabulating amnesic patients, and 10 healthy controls. The confabulating patients showed confabulations across all story types. In particular, they produced positive/pleasant memories in response to negative stories about themselves, i.e. confabulations, which the authors interpreted in terms of a motivational bias to confabulation. However, others have found that, although confabulations often have a strong affective flavour, this can be either positive or negative in valence (Metcalfe et al., 2010; Bajo et al., 2010).

Interactionist (multifactorial) theories have emphasised a number of factors. For example, Johnson et al. (1997) argued (on the basis of a single-case study) that confabulation is likely to occur where there is a combination of a vivid imagination, the inability to retrieve autobiographical memories systematically, and a source-monitoring impairment. Likewise, Kopelman et al. (1997) found that confabulation can occur across episodic, personal semantic, and semantic memories. Confabulations involving temporal context memory errors were especially prevalent in episodic memory; perseverations accounted for many of the confabulations within semantic memory; and other confabulations appeared to be instantaneous, unchecked responses to immediate social and environmental cues.

2.5. Summary

In summary, within the anterograde amnesia of the Korsakoff syndrome, short-term/working memory and short-term forgetting are relatively preserved. Recall and recognition memory are both generally affected (in the absence of giving very prolonged exposure times to the patients on recognition testing). There is a disproportionate deficit of temporal context memory, with spatial context memory more variably affected. The anterograde amnesia appears to be attributable to damage in the mammillary body/mammillo-thalamic tract/anterior thalamic circuitry, rather than to pathology in the medial dorsal nuclei of the thalamus, although there are conflicting claims with respect to this.

With respect to retrograde amnesia, there is an extensive retrograde memory impairment, going back 20–25 years or more, with a 'steep' temporal gradient in most studies, indicating relative sparing of early memories. Within this retrograde amnesia, there is a disproportionate impairment in dating events, even when the events themselves have been correctly identified. The retrograde

amnesia may be attributable to damage to thalamic-frontal projections (superimposed on the mammillary-thalamic pathology), giving rise to a retrieval deficit.

Spontaneous confabulation is seen in the acute confusion of Wernicke's encephalopathy, but is less commonly seen in the more chronic phase of the Korsakoff syndrome unless there is superimposed, concomitant ventro-medial and/or orbito-frontal damage. It seems likely that various deficits can contribute to its occurrence, including temporal context memory confusions, deficits in monitoring and editing out errors, and inappropriate perseverations. The confabulations often have a strong affective flavour, which may be positive and self-referential, but this is not necessarily always the case.

3. Thalamic amnesia

3.1. Introduction

Various clinical and neuropsychological studies have established that thalamic infarction can give rise to an amnesic syndrome (e.g. Speedie and Heilman, 1982; Guberman and Stuss, 1983; Winocur et al., 1984). However, there have been divergent accounts of the blood supply to thalamic nuclei (Von Cramon et al., 1985), and relatively few good anatomical descriptions of the key sites of the lesions in amnesia (Castaigne et al., 1981; Mori et al., 1986; Graff-Radford et al., 1990).

Animal studies established the connection between the hippocampus and the anterior and latero-dorsal nuclei of the thalamus, passing through the fornix, mammillary bodies, and the mammillo-thalamic tract (Aggleton and Saunders, 1997). There was a second route from the hippocampus via the fornix to the anterior and latero-dorsal thalamic nuclei, which did not pass through the mammillary bodies. A third neural pathway conveyed fibres from the amygdala and perirhinal cortex via the inferior thalamic peduncle and the internal medullary laminae to the medio-dorsal thalamic nuclei (Aggleton and Saunders, 1997; Graff-Radford et al., 1990; Carlesimo et al., 2011). Recent research has attempted to disentangle how these pathways and nuclei are related to differing aspects of memory function.

3.2. Neuroanatomical and cognitive considerations

The ventral thalamus is principally supplied by the polar and paramedian arteries, the former in a more anterior distribution, although there is substantial variability (Von Cramon et al., 1985). On the basis of CT images of six patients with ventral thalamic infarcts, four of whom suffered from chronic amnesia, whereas two showed no obvious memory impairment, Von Cramon et al. (1985) argued that damage to the mammillo-thalamic tract and the ventral part of the lamina medullaris interna was critical to the development of an amnesic syndrome, whereas damage to the medio-dorsal nuclei in the absence of pathology in these other structures did not produce amnesia. While MRI studies have also described patients with discrete focal thalamic lesions (Van der Werf et al., 2003; Pergola et al., 2012; see below), the few PET studies show variable findings from focal thalamic and posterior cingulate change (Clarke et al., 1994) to widespread unilateral cortical hypometabolism (Baron et al., 1986).

Van der Werf et al. (2003) examined 22 cases of thalamic infarction. Of these, 10 were judged to have 'clean' lesions without pathology elsewhere. Within this group, three cases had an amnesic syndrome, all of whom showed damage to the mammillo-thalamic tract within the left and right ventral anterior thalamus. When patients with more widespread pathology were also included, there were a further four patients who had suffered from a dense

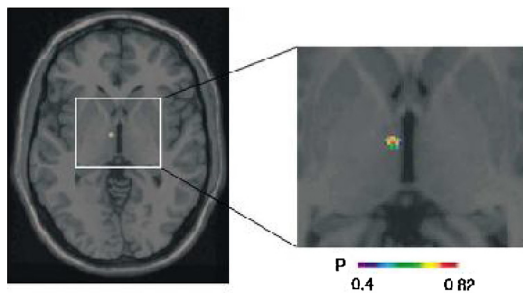


Fig. 3. Van der Werf et al., 2003: Critical site for anterograde amnesia.

amnesia, and all of these had lesions encompassing the mammillo-thalamic tract. Fig. 3 shows the overlap of lesions of patients with an amnesic syndrome, corrected for the lesion distribution of patients without an amnesic syndrome. However, one patient with pathology in the left mammillo-thalamic tract did not show an amnesic syndrome.

In a review of 83 patients with thalamic infarction from 41 scientific papers, Carlesimo et al. (2011) reported that 52 out of 55 patients (95%) with mammillo-thalamic tract damage were described as suffering from anterograde amnesia, compared with only 13 out of 28 patients (46%) without mammillo-thalamic tract damage. By contrast, involvement of the medio-dorsal nucleus of the thalamus did not significantly predict anterograde amnesia. Retrograde amnesia had less commonly been reported, but was identified in 13 out of 14 patients with mammillo-thalamic tract involvement, compared with 15 out of 28 cases without such pathology. The authors concluded that the mammillo-thalamic tract (and indirectly the anterior thalamic nuclei, to which the mammillo-thalamic tract projects) plays a critical role in the genesis of episodic memory impairment in these patients. The authors postulated that the anterior nuclei are part of the 'extended hippocampal system' (Aggleton and Saunders, 1997; Aggleton and Brown, 1999), mediating explicit recall memory, and that a second circuit (from perirhinal cortex to the medio-dorsal nuclei) is involved in the familiarity components of memory.

Rather different results have been reported by the Bochum group. Zoppelt et al. (2003) compared recollection and familiarity memory performance in patients with medio-dorsal thalamic lesions and those with ventro-lateral thalamic lesions. There were no significant differences in the memory performance of these two groups, except for familiarity estimates which were more impaired in the ventro-lateral group. Both lesion groups showed impairment in recollection memory. More recently, Pergola et al. (2012) compared nine patients with ischaemia in the paramedian artery distribution, affecting the parvocellular medio-dorsal nucleus, with eight patients with damage to the polar (tuberothalamic) artery, which preferentially supplies the ventral anterior nucleus and the mammillo-thalamic tract. On tests of recognition memory, both patient groups were significantly impaired. Cued recall performance was significantly related to volume loss in the parvocellular medio-dorsal nucleus, suggesting a role of this nucleus in recall memory and recollection, inconsistent with the Aggleton and Brown (1999) hypothesis. The authors noted that there are important connections between this brain region and the dorso-lateral prefrontal cortex. They concluded that the parvocellular medio-dorsal nucleus is critical for recall and recollection memory, rather than just contributing to recognition/familiarity-based memory. In a subsequent functional imaging study in healthy participants, Pergola et al. (2013) showed that the medio-dorsal thalamic/prefrontal cortical network was activated during successful encoding and retrieval of learned associations, again indicating a role of this system in recall and recollection.

3.3. Neuropsychological pattern of impairment

3.3.1. Anterograde amnesia

A detailed investigation of the neuropsychological pattern of thalamic amnesia was reported by Winocur et al. (1984). These authors investigated patient B.Y., using the techniques available at that time. They showed that, on the Brown-Peterson test of short-term forgetting with a 4-s presentation of stimuli, B.Y. showed normal retention up to and including a 9-s delay, but severely impaired retention at 18 s. On a serial position curve for immediate free recall of words, B.Y. showed the expected primacy and recency effects (with preserved retention), but impaired recall for words at intermediate positions, compared with a matched control. On delayed free recall, B.Y. showed impairment, relative to the control, at all serial positions. On the Warrington forced-choice Recognition Memory Test, B.Y. was impaired at both words and faces; but, in hindsight, his scores suggest that there may have been relative sparing in his performance on recognition memory, compared with his recall memory performance. On a test of famous faces (from the 1940s to 1980), B.Y. performed normally at all time-periods. In summary, the findings suggested preserved short-term retention (up to approximately 9 s), impaired new episodic learning on both recall and recognition memory testing (but with, perhaps, relative sparing of performance on recognition memory testing), and an absence of any retrograde amnesia (but this was tested on only one 'semantic' test).

In a single-case report, Edelstyn et al. (2006) described a patient with a left medio-dorsal thalamic lesion and bilateral involvement of the dorso-lateral thalamic nuclei. The patient was presented with 50 famous names, 50 artists, or 50 unknown names in separate 'study' phases. After each presentation, the patient was then given a Yes–No recognition test, in which the 50 studied names were intermingled with 50 distractors of the same class. In addition, the patient had to make remember/know judgements following each positive response. In terms of discrimination accuracy on the (yes/no) recognition memory test, and estimates of conscious recollection ('remember' judgements), the patient was severely impaired for the artist and the other famous names, relative to controls. However, in terms of familiarity ('know' judgements), the patient showed minimal impairment for both artist names and other famous names. Similarly, Kishiyama et al. (2005) described a patient with bilateral anterior and medial thalamic lesions, who showed more severe deficits in recall than in recognition memory. Associated with this, there was a severe deficit in recollection, and a smaller but consistent impairment in familiarity-based recognition memory as well. By contrast, Cipolotti et al. (2008) examined two patients with thalamic lesions. Both had involvement of the left anterior and medio-dorsal nuclei; one had right anterior and the other right medio-dorsal pathology. However, on the Recognition Memory Test (Warrington, 1984) and the Doors and People Test (Baddeley et al., 1994), both visual and verbal recognition memory were severely affected in both patients, as well as recall memory.

3.3.2. Retrograde amnesia

Retrograde amnesia appears to have been less frequently studied in thalamic patients than in the Korsakoff syndrome. In their small series, Graff-Radford et al. (1990) reported that one of their patients had a 'temporally extensive' retrograde amnesia; another patient was "probably" normal; and two other patients were normal in terms of performance on remote memory tests of famous faces and famous events. Clarke et al. (1994) described a 54-year-old patient who suffered an acute unilateral left polar thalamic infarct. Autobiographical memory and recent public events were assessed on an informal interview. In terms of events for which the patient had absolutely no recollection, her retrograde amnesia

Table 1
Major neuropsychological and neuroimaging findings in Korsakoff patients and thalamic infarction cases.

Neuropsychology	Korsakoff patients	Thalamic infarct patients
Primary/short-term memory		
Traditional measures	Intact	Intact
'Working memory' measures	All components impaired but no worse than non-Korsakoff alcoholics	Not tested
Anterograde episodic memory		
Recall/recollection	Severely impaired	Severely impaired
Recognition/familiarity	Impaired, but can be compensated by prolonged exposure times	Spared in some studies; impaired in others
Context memory	Temporal context memory always affected; spatial more variable	Recollection deficit implies impairment, but less specifically studied than in Korsakoff's
Retrograde amnesia	Invariably present and usually prolonged (20–25 years) with a temporal gradient	Present in approximately one-third of patients, sometimes 'extensive', sometimes brief (1–10 years)
Confabulation	Seen in acute confusional phase (Wernicke), but spontaneous confabulation in chronic phase only if extensive frontal or ventro-medial frontal damage. Mechanism controversial	Seldom if ever reported
Neuroimaging		
MRI		
Principal findings	Atrophy in thalami, mammillary bodies and frontal cortex	Critical lesions have been reported in the anterior nuclei, mamillo-thalamic tract and medio-dorsal nuclei. May be unilateral or bilateral
Associated findings	Atrophy in hippocampi (varying severity), amygdala, and cerebellar vermis	
PET	Reduced metabolism in the thalami, mammillary bodies, basal forebrain/orbito-frontal cortex, retrosplenium/precuneus. Also implicated: middle cingulate gyrus, superior frontal gyrus, temporal and occipital cortex	Few studies: thalamic and retrosplenial hypometabolism implicated. Widespread unilateral cortical hypometabolism has also been reported

extended back almost exactly one year, and showed a pronounced temporal gradient. In terms of events for which the patient had partial recall, the retrograde amnesia extended back approximately 100 days, again with a temporal gradient. Recall and recognition of more remote events and famous faces were entirely normal. In their review, [Carlesimo et al. \(2011\)](#) found that 46 thalamic infarct cases had been tested for retrograde amnesia. Of these, 15 (32.6%) showed a retrograde amnesia. Autobiographical memory recall was reported to have been affected in 14 out of these 15 cases. Moreover, a temporal gradient was described in 10 out of the 15 cases, which was reported to be 'extensive' in six patients, and time-limited in four cases.

4. Korsakoff syndrome versus thalamic infarction: summary and conclusions

[Table 1](#) summarises some of the main neuropsychological and neuroimaging findings in Korsakoff patients and cases of thalamic infarction.

In terms of anterograde amnesia, thalamic infarction cases manifest many of the features of an amnesic syndrome. Some studies have reported disproportionate impairment of conscious recollection, compared with recognition/familiarity-based memory, but others have described both components of memory as being affected. By contrast, in the alcoholic Korsakoff syndrome, impairments of both recall and recognition memory are generally reported. In human studies of thalamic amnesia (unlike the animal reports), context memory seems to have been relatively unexplored. This is surprising in view of the considerable interest in this topic in the Korsakoff syndrome. In thalamic infarction, amnesia has more commonly been attributed to anterior thalamic/mammillo-thalamic tract involvement than to pathology within the medio-dorsal nuclei. However, there are conflicting reports on this, and the Bochum group have argued for an important role of the medio-dorsal nuclei in recollective memory. Conflicting findings, but with the anterior thalamic nuclei being more

commonly implicated, have also been observed in the Korsakoff syndrome.

With respect to retrograde amnesia, there are surprisingly few reports in thalamic infarction, and this, in itself, probably reflects the fact that it is less commonly implicated than in the Korsakoff syndrome. Where retrograde amnesia has been investigated, it is seen in approximately a third of cases, and is usually temporally graded. In general, retrograde amnesia extends back across a far shorter time, and is much less severe, than is typical in the Korsakoff syndrome. This is likely to be because there is less severe damage to thalamic-frontal projections, and a much lesser degree of frontal atrophy, in thalamic cases than is typically found in the Korsakoff syndrome. Likewise, *spontaneous confabulation* seems to have been seldom reported in thalamic cases. Given that spontaneous confabulation has often been attributed to specific ventro-medial and/or orbito-frontal damage (or else to widespread frontal atrophy), its absence in thalamic cases presumably reflects the fact that these regions are seldom implicated.

In conclusion, there is scope for further investigation comparing the patterns of neuropsychological deficit in thalamic infarction and Korsakoff cases. Existing findings suggest some common core findings across the two groups, particularly in anterograde amnesia. Where differences arise, particularly in retrograde amnesia, this is likely to reflect the greater degree of pathology that occurs in Korsakoff patients, extending beyond the thalamic circuitry and into the frontal lobes.

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